The 63-year-old female patient was diagnosed with primary metastatic clear cell renal cell cancer in December 2007. She was found to have a right renal tumour with invasion of the right renal vein and the vena cava, bilateral adrenal metastases, multiple lung metastases and a solitary lytic bone metastasis in the left 10th rib laterally.

The patient was treated with sunitinib 50 mg 4 weeks on/2 weeks off starting in January 2008.

A computed tomography (CT) scan after 4 weeks of treatment showed decrease in size of all involved tumour sites. Response to treatment was maintained and last seen on a CT scan in August 2008.

In November 2008, obvious disease progression was demonstrated on CT with progression of the primary tumour, both adrenal metastases and the lung metastases and new mediastinal lymph-node metastases (Figures 1 and 2).

Treatment was therefore stopped and the patient was considered for participation in the expanded access trial with RAD001, a novel orally available mammalian target of

Figure 1. Lung metastases.

Figure 2. Kidney tumour.

We report a rare case of regression of metastatic renal cell cancer after stopping treatment with the tyrosine kinase inhibitor sunitinib.

‘Sunitinib withdrawal phenomenon’ or spontaneous regression in renal cell cancer
rapamycin inhibitor. At this time, she was symptomatic from the bone metastasis in her rib and fatigue.

A screening CT scan was carried out for trial purposes at the end of December 2008, which at this point revealed disease regression in all tumour locations—the right kidney (6.3–4.2 cm), both adrenals (3.7–1.5 cm and 2.8–1.7 cm), lymph nodes and the lung—compared with the scan from November 2008.

We decided not to treat the patient systemically and postponed enrolment on the trial and adopted an active surveillance approach. A repeat CT evaluation in mid-February 2009 (Figures 3 and 4) confirmed disease regression in the lung and the right kidney.

Fatigue has resolved since stopping sunitinib. Due to persisting pain in the 10th rib, we have decided to give palliative analgetic radiotherapy to this site and continue the active surveillance strategy otherwise.

discussion

Spontaneous regression in renal cell cancer is a well-recognised phenomenon and has been reported before [1].

In many case reports of the so-called spontaneous regression, the primary tumour is surgically removed [2], irradiated [3] or ablated [4], but elimination of the primary tumour does not seem to be necessary since regressions are also reported in the absence of nephrectomy or other primary tumour manipulations [5].

The mechanism underlying spontaneous regression in renal cell cancer patients remains unclear, although immunologic effects as a basis of this phenomenon have been postulated.

Regression of metastatic clear cell renal cell carcinoma without active treatment and after progression on treatment with a tyrosine kinase inhibitor has not been reported before.

In contrary, discontinuation of vascular endothelial growth factor (VEGF) inhibition has been feared to accelerate angiogenesis and tumour growth due to simultaneous induction of VEGF and other proangiogenic pathways. And there is preclinical evidence to support this theory [6]. The key and ongoing role of VEGF in angiogenesis provided the rationale for continuous anti-VEGF therapy until, and possibly beyond, disease progression [7].

However, it may be hypothesised that in our case either stopping the tyrosine kinase inhibitor had a positive effect or spontaneous regression occurred.

In analogy to prostate cancer, where androgen receptor mutant forms can proliferate and avoid apoptosis by using antiandrogens as substitute for androgens [8] and withdrawal of these antiandrogens can promote disease regression, VEGF and platelet-derived growth factor receptor mutations or subtle modifications may occur in renal cell cancer and initiate a switch from antagonistic to agonistic.

There is also a complex crosstalk between VEGF receptors and it is perceivable that interfering with these regulatory mechanisms can have anti- as well as proangiogenic effects.

In our case, the CT scan was only carried out for trial requirements and we would have attributed the regression to treatment with RAD001 without this repeat imaging. Such regressions may very well occur more frequently but remain undetected due to instant initiation of a second-line therapy without new staging since so many treatment options in renal cell cancer are available now.

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references


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